REMARKS

Applicants respectfully request consideration of the application in view of the foregoing amendments and the following remarks.

Claim 6 is amended herein to more distinctly point out the subject matter of Applicant's invention. Specifically, the amendment is made to show that the HER2 protein comprises the extracellular and transmembrane domains of HER2, but not the intracellular domain. Support for the amendment can be found, *inter alia*, on page 7, lines 28-32.

Claim 9 is amended herein to indicate that the host cell is "an isolated" host cell. Support for the amendment can be found, *inter alia*, on page 15, line 31 to page 16, line 14 of the Specification. No new matter has been added.

Claims 1-5, 11, 13, and 15-24 are canceled herein as being drawn to a non-elected invention. These claims are canceled without prejudice to pursuing the subject matter of said claims in a later filed divisional application.

Rejection under 35 U.S.C. § 112, First Paragraph

Claims 9 and 12 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Specifically, the Office Action states that claims 9 and 12 do not indicate that the host cells are isolated or in culture, and, as such, encompass transgenic animals and plants and the production of human HER2/neu protein therein.

Applicants disagree with this rejection, but nonetheless submit that the rejection is moot. Applicants have amended claims 9 and 12 herein to indicate that the host cell is "an isolated" host cell in an effort to advance prosecution of this case. Accordingly, Applicants respectfully request the reconsideration and removal of the instant rejection.

Rejection under 35 U.S.C. § 103

Claims 6-10 and 12 are rejected under 35 U.S.C. §103(a) as being unpatentable over the teachings of Cheever *et al.* (U.S. Patent No. 5,869,445) in view of Foy et al. (*Vaccine*, 19: 2598-2606 (2001)), Ikemura *et al.* (*Mol Biol. Evol.* 2: 13-34 (1985)), and Nakamura et al. (*Nucleic Acids Research*, 27: 292 (1999)). The teachings of these references are alleged to render the subject matter of claims 6-10 and 12 obvious. Applicants respectfully traverse.

The Office Action states that Cheever et al. discloses the amino acid sequence SEQ ID NO:2, which contains the instant SEQ ID NO:14. The Office Action further states that

Cheever *et al.* discloses "modifying the nucleic acid sequence to employ codon bias for recombinant production of the protein in a desired host." It is alleged that it would have been obvious to use human codons for the sequence of Cheever et al. It is further alleged that Ikemura et al. and Nakamura et al. demonstrate that codon usage in different species "would have been well known to those of ordinary skill in the art."

Applicants note that the initial burden of presenting a prima facie case of obviousness rests on the Examiner. *In re Oetiker*, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). To establish a prima facie case of obviousness, the Examiner must show: (1) a suggestion or motivation in the prior art to modify or combine references; (2) a reasonable expectation of success and (3) that all of the claim limitations are taught or suggested by the prior art. MPEP § 2143. Both the suggestion to make the claimed combination and the reasonable expectation of success, must be found in the prior art, not in Applicant's disclosure. *See, e.g. In re Vaeck*, 20 USPQ2d1438 (Fed Cir. 1991). Only after a proper prima facie case of obviousness is established does the burden of rebutting the same shift to the Applicants.

In the present case, Applicants assert that the Office Action fails to establish a prima facie case of obviousness because, given the prior art, one of skill in the art would not have had a reasonable expectation of success in developing the instant invention, in contrast to the position taken in the Office Action. Specifically, it is Applicants' position that The Office has failed to provide evidence that the claimed invention "does no more than yield predictable results."

At the outset, Applicants refute two points in the following statement set forth by the office: "[i]t would have been obvious to use human codons for the sequence of Cheever et al." *See* Office Action at page 4, lines 1-2. First, Applicants note that SEQ ID NO:14, although contained within SEQ ID NO:2 as are hundreds of other shorter sequences, is not itself disclosed in Cheever. Second, Applicants assert that the cited art does not contain a suggestion to optimize the codons of HER2, or of HER2ECDTM, with human-preferred codons to arrive at the instant invention. Cheever merely makes a general statement that "substitutions may be made to enhance expression, primarily to avoid secondary structure loops in transcribed mRNA...or to provide codons that are more readily translated by the selected host, such as the well-known *E. coli* preference codons for *E. coli* expression." *See* Cheever *et al.* at column 9, lines 46-51. Cheever does not specifically suggest replacement of the codons of HER2, which is a human gene, with human-preferred codons. In fact, although codon-optimization was a known technique at the time of filing, it was not suggested that this technique be used with HER2 or with human tumor-associated antigens for increased expression in human host cells.

Additionally, Cheever *et al.* did not attempt to codon-optimize a HER2 gene for optimal expression in any type of host cell, and therefore, did not show that it was successful.

Moreover, Applicants respectfully disagree with the notion that the currently claimed invention yields predictable results given the uncertainty in the art. More specifically, it is known that codon optimization is not always successful at increasing the expression of other genes. *See, e.g.* Alexeyev et al. *Biochim. Biophys. Acta* 1419: 299-306 (1999, attached herein as Exhibit "A") where codon optimization of the gene encoding *Rickettsia prowazekii* protein Tlc for optimal expression in an *E.coli* host had no effect on expression (see Abstract, wherein it is stated: "Although codon usage in R. prowazekii is very different from E. coli, the optimization of the codon usage by itself was insufficient to improve expression.") *See also* Coulombe *et al* (Gene 46: 89-95 (1986), attached herein as Exhibit "B"), wherein the authors made several changes to the human interferon (IFN) gene, including codon optimization, and drew the following conclusion (see page 94, column 1, first full paragraph):

> It has been proposed that codon usage and the presence of complementary and repeated sequences in mRNA could be important in regulation of translation, the former through the relative frequency of different tRNA forms (Osterman, 1979), and the second through the generation of secondary structure (Edge et al., 1981). The results presented here show that, in the case of the HuIFN-α1 gene, these features are not essential for expression.

One reason that codon optimization is not always successful is that expression levels of some genes is limited by factors other than or in addition to suboptimal codon usage, such as the presence of negative regulatory sequences within a gene's untranslated region, or suboptimal sequences within the 5' proximal region. In such cases, codon usage may have no effect on expression, or have some effect, but not enough to overcome the additional factors that are controlling expression in the particular gene, or not enough to lead to the desired expression level. *See, e.g.* Kim *et al. Gene* 199: 293-301 (1997), wherein the authors compare the expression of different modified EPO genes in mammalian cells, which contain human optimized codons, yeast optimized codons, or a hybrid of both. The authors conclude that in the case of EPO, the highest expression was obtained with a codon-usage hybrid gene "comprising the 5' segment downstream of the initiator codon with the yeast codon usage and the rest with the human codon usage." They summarize their conclusions by stating that "our results suggest that the linear sequence between the promoter and the 5' proximal region of a gene plays an important role in achieving high-level expression in mammalian cells." (*See* last sentence of

Abstract). Interestingly, the highest expressing version of EPO was one in which this "important region" contained yeast-preferred codons.

Thus, consistent with the discussion, *supra*, Applicants respectfully submit that articles describing codon-optimization of genes other than HER2 would be irrelevant because the solution to achieving high enough expression levels of a particular gene to be clinically significant differs in the case of each gene, depending on the actual cause of low expression levels. For this reason, the mere knowledge that codon optimization was used for other genes is not sufficient to establish an expectation of success for our specific HER2 and HER2ECDTM genes. Thus, Applicants respectfully submit that Applicants results were not predictable based on the prior art.

In accordance with the claimed invention, the Applicants have shown shows that codon optimization of a gene encoding HER2ECDTM (SEQ ID NO:14, encoded by SEQ ID NO:9) for high level expression in a human host cell, leads to a gene that is expressed more efficiently than the corresponding wild-type sequence. It was also shown that the optimized truncated HER2ECDTM gene, which encodes a protein lacking the intracellular domain of HER2, induced a higher anti-p185 (a.k.a. HER2 protein) cell-mediated response in mice than that induced by a optimized gene encoding full-length HER2, as measured by IFN-gamma ELISPOT analysis (see EXAMPLE 14 and FIGURE 8 of the Specification). These results suggest that codon-optimized HER2ECDTM would be a good candidate for a DNA-based vaccine in animals overexpressing HER2, which was not suggested by Cheever et al. or Foy et al. These deficiencies are not remedied by Ikemura *et al.* and Nakamura *et al.*, which were cited to show that codon usage in different species was known at the time of filing. Applicants do not disagree that codon usage in different species was known at the time of filing. However, Applicants assert that the usefulness of codon optimization was not predictable, as stated, *supra*.

As such, Applicants assert that claims 6-10 and 12 are not obvious over the cited prior art teachings. Accordingly, Applicants respectfully request that the rejection of these claims under 35 U.S.C. § 103 be removed and the claims allowed.

Summary

Applicants assert all claims are in condition for allowance and a favorable action on the merits is earnestly solicited.

If the Examiner believes that a telephone conference would be of value, he is requested to call the undersigned attorney at the number listed below.

Respectfully submitted,

By _____

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